

# Self-recognition in helicate self-assembly: Spontaneous formation of helical metal complexes from mixtures of ligands and metal ions

(programmed supramolecular systems/polynuclear metal complexes/instructed mixture paradigm)

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**ABSTRACT** On treatment with copper(I) ions, mixtures of the [oligo(2,2′)-bipyridine] strands 2–5 yield spontaneously the double helicates  $^2\mathcal{H}(2)$ – $^2\mathcal{H}(5)$  without significant crossover. Similarly, when a mixture of the two tris-bipyridine ligands 1 and 3a (containing different substitutions) is allowed to react with copper(I) and nickel(II) ions, only the double helicate  $^2\mathcal{H}(3a)$  and the triple helicate  $^3\mathcal{H}(1)$  are formed. Thus, these systems undergo self-assembly of helicates with self-recognition. The process represents a self/nonself-discrimination involving the preferential binding of like metal ions by like ligand strands in a mixture to selectively assemble into the corresponding helicates. In a broader perspective, these results point to a change in paradigm from pure compounds to instructed mixtures—that is from seeking chemical purity to designing programmed systems composed of mixtures of instructed components capable of spontaneously forming well-defined superstructures through self-processes.

Self-assembly and self-organization have rapidly grown into a main theme of supramolecular chemistry (1–4). Such is the case in particular for inorganic self-assembly as expressed in the spontaneous formation of double- and triple-helical multinuclear metal complexes, termed helicates, from two or three oligobipyridine (bpy in complexes) strands (5–7) or related ligands (ref. 8 and references therein and 9) wrapping in helical fashion around suitable metal ions.

It is of special importance to investigate rigorously the physicochemical features of helicate formation as a case study of the self-assembly process itself as well as the relationship to biological self-assembling systems. It has thus been shown that, in addition to the specific structural and complexation properties of helicates, their formation occurs with positive cooperativity (10, 11).

We now report another basic feature characterizing helicate self-assembly as a programmed supramolecular process, termed “self-recognition”—the recognition of like from unlike, of self from nonself—embodied in the spontaneous selection and preferential binding of like metal ions by like ligands in a mixture. In the present experiments, selective formation of helicates was obtained in mixtures of the oligobipyridine [oligo(2,2′)-bipyridine] strands 1–5 and suitable metal ions (Figs. 1 and 2).

## MATERIALS AND METHODS

**Ligands and Complexation Experiments.** The synthesis of the unsubstituted 2a–5a (5, 6), the CONEt<sub>2</sub> 4,4′-disubstituted 2b–5b (12), and the COOR 4,4′-disubstituted 2c–5c (10, 12) oligobipyridine strands as well as ligand 1 (7) has been described.

The formation of the Cu<sup>I</sup> double helicates  $^2\mathcal{H}(2)$ – $^2\mathcal{H}(5)$  has been reported for the unsubstituted ligands 2a–5a (4, 5) and for 3c (10). The substituted analogues of series b and c are obtained by similar procedures.

The experiments involving various mixtures of ligands 2–5 (series a–c) (see Figs. 4 and 5) have been performed under analogous conditions: treatment of a solution of a mixture of ligands with a small excess of [Cu(CH<sub>3</sub>CN)<sub>4</sub>]BF<sub>4</sub> (or PF<sub>6</sub>) in CH<sub>3</sub>CN leads to the rapid formation of the complexes with the deep orange-red color characteristic of [Cu(bpy)<sub>2</sub>]<sup>+</sup> species. The generation of the triple helical complex  $^3\mathcal{H}(1)$  has been described (7).

**Simultaneous Formation of the Double Helicate  $^2\mathcal{H}(3a)$  and of the Triple Helicate  $^3\mathcal{H}(1)$ .** Under nitrogen atmosphere, 15.6 mg (28.5 μmol) of 1 and 11.0 mg (19.0 μmol) of 3a are suspended in a mixture of 16 ml of ethylene glycol and 2 ml of acetic acid. The mixture is heated to 180°C (bath temperature) with stirring. As soon as the ligands dissolve completely, a solution containing 10.4 mg (28.5 μmol) of Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and 9.3 mg (28.5 μmol) of Cu(ClO<sub>4</sub>)<sub>4</sub>·4CH<sub>3</sub>CN in 0.5 ml of CH<sub>3</sub>CN is added dropwise. The dark red solution obtained is stirred at 180°C (bath temperature) under nitrogen for 1 h and then cooled to room temperature. After addition of 60 ml of diethyl ether, two liquid phases appear. Tetrahydrofuran is added with stirring until one single liquid phase is obtained. The orange precipitate is centrifuged off, washed with ether, and vacuum-dried to yield 39 mg, which corresponds to 100% based on the exclusive formation of unsolvated  $^2\mathcal{H}(3a)$  and  $^3\mathcal{H}(1)$ . This product was used as obtained for the physicochemical measurements (NMR, MS). TLC on SiO<sub>2</sub> with an eluent of acetonitrile/water/saturated aqueous KNO<sub>3</sub>, 5:4:1 (vol/vol), indicated that it contained only the two helicates  $^2\mathcal{H}(3a)$  and  $^3\mathcal{H}(1)$  as shown by comparison with pure samples of these two complexes; the retardation factor, *R<sub>f</sub>*, is 0.70 for  $^2\mathcal{H}(3a)$  and 0.50 for  $^3\mathcal{H}(1)$ .

## RESULTS AND DISCUSSION

**Self-Recognition in Double-Helicate Formation.** The spontaneous formation of a double helicate,  $^2\mathcal{H}$ , from a 6,6′-connected oligobipyridine ligand and Cu<sup>I</sup> ions is a clean process yielding only the corresponding helicate, no other species being observed (1, 2, 5, 6). The question one may ask is what will happen when a mixture of several oligobipyridine strands of different lengths is treated with Cu<sup>I</sup>. Will only helicates containing identical strands be formed or will more or less ill-defined mixtures be obtained?

Thus, mixing the ditopic 2 and tritopic 3 oligobipyridine species could give a mixture containing either only the discrete helicates  $^2\mathcal{H}(2)$  and  $^2\mathcal{H}(3)$  or also other mixed species such as a double-helical complex of [(2)<sub>3</sub>(3)<sub>2</sub>Cu<sub>6</sub>]<sup>6+</sup> composition (by a vernier mechanism; Fig. 3) as well as a variety of other compounds. When a mixture of 3 equivalents of 2a and of 2 equivalents of 3a was treated with excess [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> in

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Abbreviation: FAB, fast atom bombardment.

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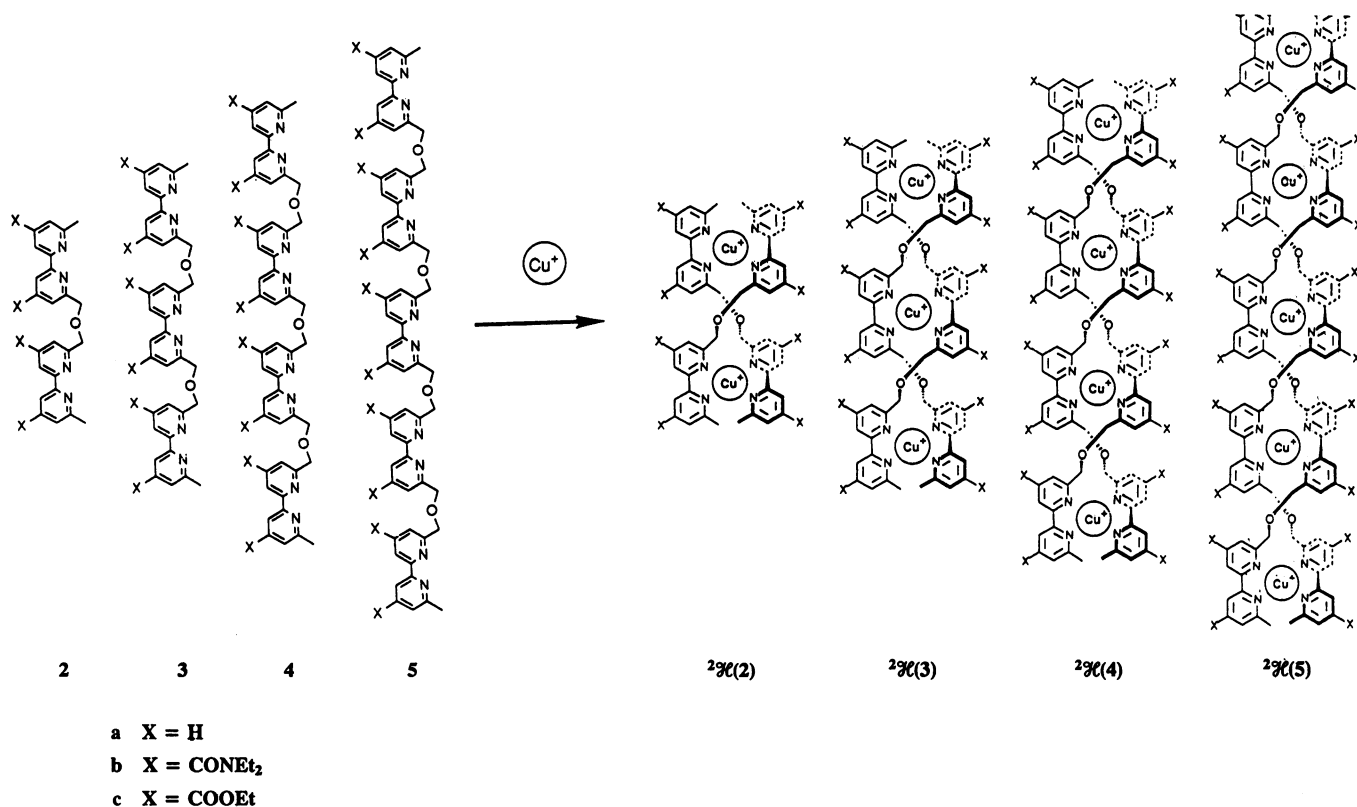


FIG. 1. Self-recognition in the self-assembly of the double helicates  $2H(2-5)$  from a mixture of the oligobipyridine strands 2–5 and  $Cu^I$  ions. ( $BF_4^-$  or  $PF_6^-$  anions omitted).

$CH_2Cl_2$ , a compound was isolated that was found by 400-MHz  $^1H$ -NMR spectroscopy (in  $C^2H_3CN$ ) to contain only the helicates  $2H(2a)$  and  $2H(3a)$  (in a 3/2 ratio), no other species being observable (Fig. 4). Similarly, a mixture of 2b and 3b yielded only  $2H(2b)$  and  $2H(3b)$  as indicated by  $^1H$ -NMR spectroscopy; the fast atom bombardment (FAB) positive-ion mass spectrum showed the peaks to correspond to  $(2H(2b)-PF_6)^+$ ,  $m/z = 1829.9$ , and to  $(2H(3b)-PF_6)^+$ ,  $m/z = 2831.3$ ; no peak due to mixed species was found.

A 2:1 mixture of 2b + 4b afforded only a 2:1 mixture of  $2H(2b)$  and  $2H(4b)$ , and no mixed-ligand complex  $2H(2b)_2(4b)$

or other complex was observed. Such a 2:1 species would be expected to be destabilized by steric interaction in the center of the structure, in particular between the  $CH_3$  groups of the two (2b) units. Further, formation of this 2:1 species would also be entropically disfavored since it would lead to a smaller number of particles than in the case of a  $2H(2b)/2H(4b)$  mixture.

Finally, a mixture of the four amide strands 2b (1 mg), 3b (1.5 mg), 4b (2 mg), and 5b (2.5 mg) was treated with excess  $[Cu(CN_3CN)_4]BF_4$  in  $C^2H_3CN$ . The 500-MHz  $^1H$ -NMR spectrum showed at first a very complicated pattern indicating a

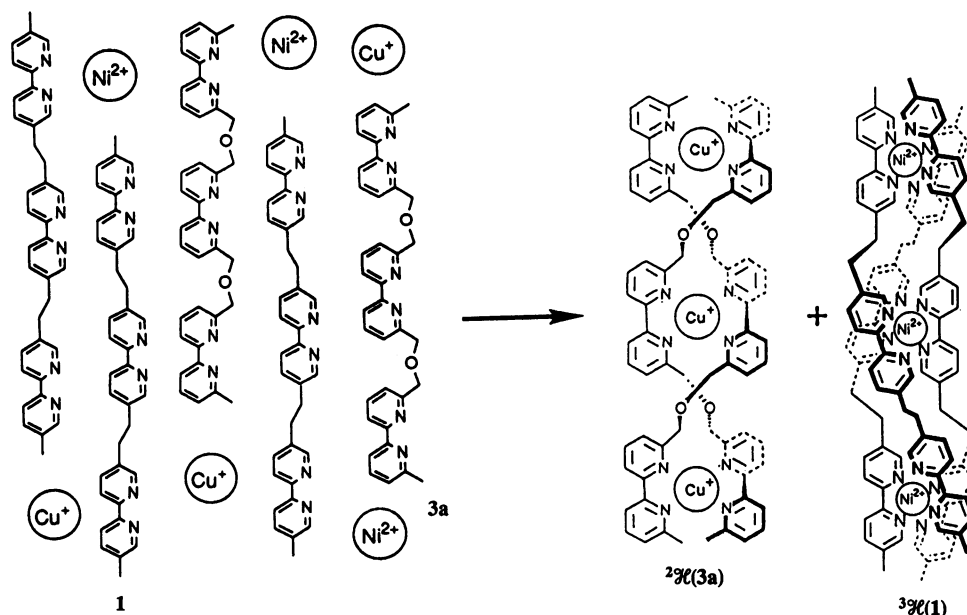


FIG. 2. Self-recognition in the self-assembly of the double helicate  $2H(3a)$  and the triple helicate  $3H(1)$  from a mixture of the oligobipyridine strands 1 and 3a and of  $Cu^I$  and  $Ni^{II}$  ions ( $ClO_4^-$  anions omitted).

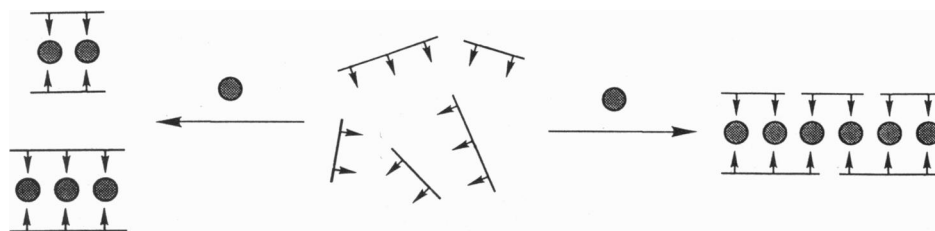


FIG. 3. Possible formation of either a mixture of helicates  $^2H(2)$  and  $^2H(3)$  (Left) or a mixed helicate  $[(2)_3(3)_2Cu_6]^{6+}$  by a "vernier" type mechanism (Right) from a mixture of the oligobipyridine strands 2 and 3 and  $Cu^I$  ions (shaded circles).

complex mixture of compounds. This was not unexpected, since the formation of the substituted pentahelicate  $^2H(5b)$  had been found to proceed very slowly, over several days, probably because of a slowing down of the rates of wrapping and unwrapping by steric effects arising from the  $CONEt_2$  substituents. The spectrum progressively cleared up and finally displayed a pattern whose peaks could all be attributed to the helicates  $^2H(2b)$ ,  $^2H(3b)$ ,  $^2H(4b)$ , and  $^2H(5b)$ . The spectrum (Fig. 5) looked somewhat less clean than that obtained in the experiments described above, indicating that some mixed species were perhaps present, but the helicates were clearly overwhelmingly formed (Fig. 1). The FAB positive ion mass spectrum (Fig. 6) showed the strongly predominant peaks of the tri-, tetra-, and pentahelicates; the simultaneous observation of all four helicates was not possible in the conditions used because of very different desorption rates.

All combinations of unsubstituted (series a) or substituted (series b) ligands tried gave the corresponding double helicates, indicating that helicate self-assembly occurred with two-by-two recognition of the ligands—i.e., with self-recognition and self/nonself-discrimination, formation of the species with like ligands being strongly preferred over species with unlike ligands.

The effect of substituents seems to indicate that recognition is highest for the unsubstituted ligands, which however have much lower solubility. With COOEt substituents, it was found that the spectrum of a mixture of 2(2c) + 3(3c) + 4(4c) + 5(5c) in  $C^2H_3CN$  to which excess  $[Cu(CH_3CN)_4]BF_4$  was added contained the expected peaks of the corresponding helicates but also weaker secondary peaks that could be due to the formation of mixed species. Other data had shown that

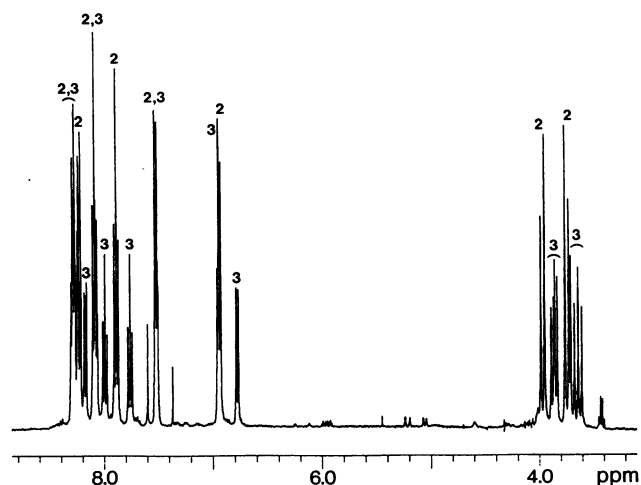


FIG. 4. The 400-MHz proton NMR spectrum of the mixture of double helicates  $^2H(2a)$  and  $^2H(3a)$  obtained from a mixture of the oligobipyridine strands 2a and 3a (molar ratio 3:2) and a small excess of  $[Cu(CH_3CN)_4]PF_6$  in  $CD_3CN$ . The notations 2 or 3 or 2,3 above the peaks indicate their assignment to the helicates  $^2H(2a)$  and  $^2H(3a)$ , respectively.

bipyridine groups bearing ester functions in 4,4' positions gave weaker  $Cu^I$  complexes. Thus, the appearance of these other species could be a result of both steric and electronic effects on  $Cu^I$  complexation and helicate formation.

**Self-Recognition in Double/Triple-Helicate Formation.** We have recently described the self-assembly of the trinuclear triple helicate  $^3H(1)$  from three oligobipyridine strands 1 presenting 5,5'-disubstitution and three octahedrally coordinated  $Ni^{II}$  ions (7). The self-assembly of the triple helix may be considered to result from the operation of the steric programme of ligand 1 through an octahedral algorithm, like the double helicates  $^2H(2)$ – $^2H(5)$  result from a tetrahedral reading of the steric information present in the ligands 2–5.

If these two types of systems are sufficiently instructed, then a mixture containing 2 equivalents of 3a, 3 equivalents of 1, 3 equivalents of  $Cu^I$ , and 3 equivalents of  $Ni^{II}$  should lead to the self-assembly of only the double helicate  $^2H(3a)$  and the triple helicate  $^3H(1)$  (Fig. 2). Indeed, when such a mixture was treated in appropriate conditions (see *Materials and Methods*), precipitation of the resulting complexes as perchlorate salts gave a quantitative yield of a product that was found by TLC to contain only the expected double and triple helicates  $^2H(3a)$  and  $^3H(1)$ . This was confirmed by MS. The electrospray mass spectrum of the precipitate contained only peaks that were also present in the mass spectra obtained for the pure double helicate  $^2H(3a)$  [ $m/z$  450.3,  $(M-3ClO_4)^{3+}$ ] and the pure triple helicate  $^3H(1)$  [ $m/z$  303.6,  $(M-6ClO_4)^{6+}$ ] (Fig. 7). In the FAB positive ion mass spectrum, the parent ion peaks [ $m/z$  = 1548.5,  $(^2H(3a)-ClO_4)^+$ ; and  $m/z$  = 2319.1,  $(^3H(1)-ClO_4)^+$ ] of both complexes were observed. The  $^1H$ -NMR spectrum was a superposition of the sharp signals of the spectrum of the diamagnetic complex  $^2H(3a)$  (5) and of the broad signals given by the paramagnetic species  $^3H(1)$  (7).

This experiment demonstrated the recognition of the tetrahedrally coordinating  $Cu^I$  ions by the 6,6'-linked tritopic bipyridine ligand 3a and of the octahedrally coordinating  $Ni^{II}$

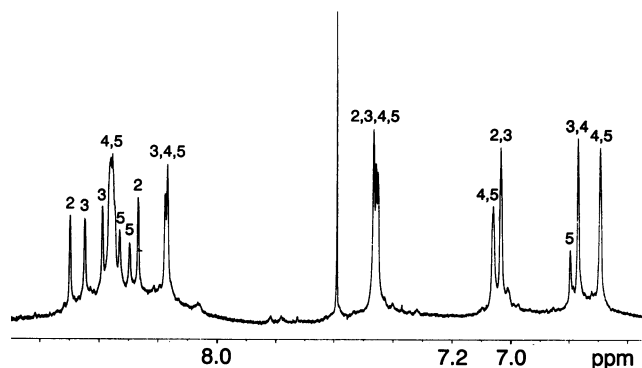


FIG. 5. The 500-MHz proton NMR spectrum of the mixture of double helicates  $^2H(2b-5b)$  obtained from a mixture of oligobipyridine strands 2b (1 mg), 3b (1.5 mg), 4b (2 mg), and 5b (2.5 mg) and a small excess of  $[Cu(CH_3CN)_4]BF_4$  in  $CD_3CN$ . The notations 2–5 above the peaks indicate their assignment to a given helicate  $^2H(2b)$ – $^2H(5b)$ .

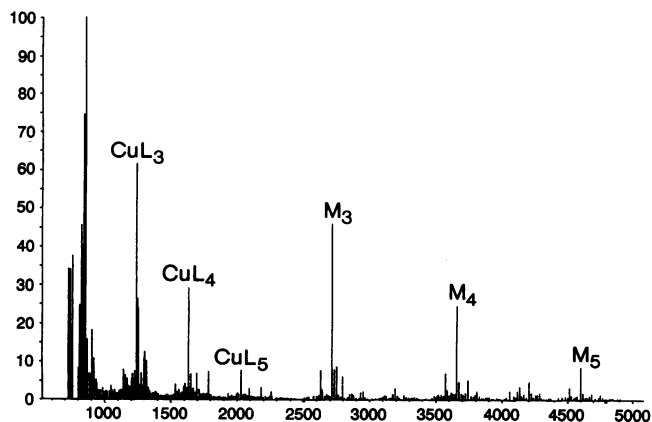


FIG. 6. FAB positive-ion mass spectrum of the mixture of helicates  $^2\mathcal{H}(2b-5b)$  obtained from a mixture of oligobipyridine strands  $[2(2b) + 3(3b) + 4(4b) + 5(5b)]$  and excess  $[Cu(CH_3CN)_4]BF_4$ . Peak assignments:  $CuL_3$  (1238.6),  $[Cu(3b)]^+$  (calc., 1238.99);  $CuL_4$  (1635.0),  $[Cu(4b)]^+$  (calc., 1635.34);  $CuL_5$  (2030.6),  $[Cu(5b)]^+$  (calc., 2031.95);  $M_3$  (2715.0),  $[Cu_3(3b)_2](BF_4)_2^+$  (calc., 2715.14);  $M_4$  (3658.3),  $[Cu_4(4b)_2](BF_4)_3^+$  (calc., 3658.25);  $M_5$  (4601.7),  $[Cu_5(5b)_2](BF_4)_4^+$  (calc., 4601.76). The simultaneous observation of the helicate  $^2\mathcal{H}(2b)$  was not possible because of very different desorption rates in the conditions used.

ions by the 5,5'-linked tris(bipyridine) strand 1, which also resulted *de facto* in the formal (metal ion-mediated) self-recognition of ligands 3a and 1 because no crossover mixed species were identified. Thus, parallel operation of the two programmed molecular systems led to the clean self-assembly of two well-defined helical complexes from a mixture of their four components in a process involving the assembly in one stroke of altogether 11 particles of four different types into two supramolecular species.

In both self-assembly experiments described here (Figs. 1 and 2), self-recognition allows the generation of the desired products from a mixture of starting compounds. These self-recognition processes as well as the recently described multi-component self-assembly of a cylindrical molecular cage (13) involve the interplay of three structural factors and two thermodynamic factors. The three structural factors are (i) structural features of the ligands (nature, number, and arrangement of the binding subunits and the nature and position of the spacers), (ii) the coordination geometries of the metal ions, and (iii) the steric and conformational effects within the different species resulting from the various possible combinations of ligands and metal ions in a given mixture. The two thermody-

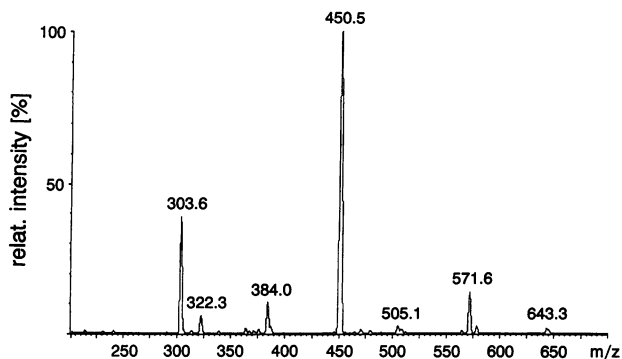


FIG. 7. Electrospray mass spectrum of the mixture of double helicate  $^2\mathcal{H}(3)$  and triple helicate  $^3\mathcal{H}(1)$  obtained from a mixture of oligobipyridine strands  $3(1) + 2(3a)$  and a mixture of metal ions  $3Cu^I + 3Ni^{II}$  as perchlorates. Peak assignments: 303.6,  $[(1)_3Ni_3]^{6+}$ ; 384.0,  $[(1)_3Ni_3(ClO_4)]^{5+}$ ; 505.1,  $[(1)_3Ni_3(ClO_4)_2]^{4+}$ ; 322.3,  $[(3a)Cu + H^+]^{2+}$ ; 450.5,  $[(3a)_2Cu_3]^{3+}$ ; 643.3,  $[(3a)Cu]^+$  or  $[(3a)_2Cu_2]^{2+}$ ; 571.6, reference (gramicidine).

amic factors are (i) the energy-related principle of "maximal site occupancy," which implies that the system evolves toward the species or the mixture of species that presents highest occupancy of the binding sites available on both the ligand and the ions [it corresponds to the formation of the highest number of coordination bonds and therefore to the more stable state of the system; full site occupancy (site saturation) is achieved in "closed" architectures]; and (ii) the entropy factor, which favors the state of the system that corresponds to the formation of the largest number of product species.

These considerations also apply to systems where binding involves interactions other than metal coordination such as hydrogen bonding or donor-acceptor forces.

## CONCLUSION

The processes considered above belong to the realm of programmed supramolecular systems (1, 2). They may be considered to result from the information processing that takes place in programmed systems based on instructed components operating through specific algorithms following given codes. The side-by-side formation of double- and triple-helical species is the consequence of the simultaneous operation of two different programs with no interference or crossover.

In this broader perspective, the results described point to the emergence of a new outlook involving a change in paradigm, from "pure compounds" to "instructed mixtures", from "unicity" (pure substance) to "multiplicity + information" (mixture of instructed components + program). Rather than pursuing chemical purity of a compound or a material, one would seek the design of instructed components which, as mixtures, would lead through self-processes to the spontaneous and selective formation of the desired (functional) superstructures. This may recall the side-by-side buildup of complex species (displaying highly integrated functions) that takes place in the self-assembly of the machinery of the living cell.

Such an evolution might also be brought in parallel with the recent development, via procedures of both chemical synthesis and molecular biology, of methods that combine generation of large repertoires of molecules with highly efficient selection procedures to obtain products presenting specific properties (refs. 14 and references therein and 15); the techniques of amplification by replication used in these methods would bear relation to the spontaneous generation of the target superstructures by the operation of self-processes. In this respect one may also point out that the very active development of the chemistry of molecular recognition processes makes the chemist able to design instructed artificial receptor molecules for the selective binding and retrieval of a well-defined substrate in a mixture of many different molecules.

One may venture to predict that this trend will represent a major line of development of chemistry in the years to come: the spontaneous but controlled buildup of structurally organized and functionally integrated supramolecular systems from a preexisting "soup" of instructed components following well-defined programs and interactional algorithms.

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